REMARKS

Applicants would like to thank the Examiner for the careful consideration given the present application. The application has been carefully reviewed in light of the Office action, and amended as necessary to more clearly and particularly describe the subject matter which applicants regards as the invention.

In this amendment, claims 28, 29, 37, 39, 48, 49 and 50 have been amended, and new claims 51-53 have been added. Thus, claims 28-33 and 35-53 are currently pending in the present application. Reconsideration of the present application is hereby requested.

In the Office action, the Examiner rejected claims 28-33 and 35-50 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In making the §112 rejection, the Examiner finds the claims to be vague and indefinite due to the lack of clarity of the phrase "predominantly of arginine" in independent claims 28, 37 and 48. In response, Applicants have amended independent claims 28, 37 and 48 to recite "comprising more than 50 percent by weight of arginine". Applicants submit that one skilled in the art would consider this range to be inherently supported by the discussion in the original disclosure of the amount of arginine present in the protein. On page 3, lines 4-6, the specification discloses the protein as consisting predominantly of arginine.

In accordance with Webster's New World Dictionary, Second College Edition, the term "predominant" means: 1. having ascendancy, authority, or dominating influence over others; superior 2. most frequent, noticeable, etc; prevailing; *preponderant*. Moreover, Roget's II: The New Thesaurus, Third Edition defines the term "predominant" as "1. Most generally existing or encountered at a given time: current, prevailing, prevalent, regnant, rife, widespread." Based on these definitions,

one skilled in the art would understand the term "predominantly" as meaning more than 50 percent. This is further supported by the case *In re Thomas*, 84 USPQ 132, 134 (CCPA 1949) wherein the CCPA specifically considered the term "consisting predominantly ". With regard to a claim limitation that read "consisting predominantly of the γ isomer", The CCPA found that "It seems reasonable to conclude that the expression "predominantly" was properly considered by the board to mean at least 50% of the isomer".

Since the specification discusses the composition of the protein in terms of weight percent, one skilled in the art would understand the phrase "consisting predominantly of arginine" (in the context of the specification) as meaning comprising more than 50 weight percent of arginine.

In making the §112 rejection with regard to claims 29, 39, 49, the Examiner finds the term "preferably" to be vague and indefinite. In response, Applicants have amended claims 29, 39 and 49 to remove the term "preferably".

In making the §112 rejection with regard to claims 48-50, the Examiner found the claims to be indefinite for failing to recite an active positive step. For this reason, the Examiner also rejected claims 48-50 under 35 U.S.C. §101, as failing to properly recite a process. In response, Applicants have amended claims 48-50 to recite an active positive step.

It is respectfully submitted that the amended claims satisfy the requirements of 35 U.S.C. §112, second paragraph and 35 U.S.C. §101.

The Examiner has rejected claims 28-33 and 35-50 under 35 U.S.C. §103(a) as being unpatentable over Wolfert et al. (Gene Therapy, 1996) in view of Hanson et al. (WO 95/25809) and further in view of Wu et al. (WO 93/04701) and Zobel et al. (Antisense Nuc. Acid Drug. Devel).

The Wolfert et al. reference discloses condensing DNA into polyelectrolyte

complexes by adding poly(L)lysine. The Wolfert et al. reference, however, further discloses that polycations are known to exert toxicities and that the concentration of electrostatic charges resulting from polyelectrolyte condensation could yield particles with extremely high charge density and possibly even increased toxicity. In this regard, the Wolfert et al. reference discloses that lower molecular weight polycations (such as 3970 Da poly(L)lysine appear to be less toxic than higher molecular weight polycations.

The Hanson et al. reference discloses solutions comprising a nucleic acid and a substance having a nucleic acid binding moiety. The Hanson et al. reference discloses that the nucleic acid binding moiety is preferably polylysine, but that other potential candidates for the nucleic acid binding moiety include Arg-Lys mixed polymers, polyarginine, polyornithine, histones, avidin, and protamines (page 23, lines 1-6). With regard to the preference for polylysine, the Hanson et al. reference discloses that poly-L-lysines may increase the efficiency of nuclear transport once inside the cell (see page 78, lines 27, 28). Beginning on page 38, line 25, the Hanson et al. reference discloses the substance with a nucleic binding moiety as being formed by galactosylating polymers of L-lysine-HBr or L-lysine-Cl. The Hanson et al. reference does not disclose the relative amounts of the polylysine and the galactose in the substance. The Hanson et al. reference makes it clear that precipitation of the nucleic acid and the substance having a nucleic acid binding moiety is not desired (see page 29, lines 3-6). Thus, chaotropic agents (salts) are added to the solution to prevent precipitation (see page 32, lines 18-21).

The Wu et al. reference discloses a solution comprising an oligonucleotide and a carrier comprising a binding agent specific to the target cell (such as a ligand) and a DNA-binding agent. The DNA-binding agent is disclosed as preferably being a polycation. Suitable polycations are disclosed as including polylysine, polyarginine,

polyornithine, and basic proteins such as histones, avidin, protamines and the like. The Wu et al. reference does not disclose the relative amounts of the DNA-binding agent and the binding agent specific to the target cell in the carrier.

The Zobel et al. reference discloses using DEAE-dextran nanoparticles as carriers for oligonucleotides. A reduced surface charge is disclosed as lowering the electrostatic repulsion of the charged DEAE groups, thereby resulting in a more compact polymer configuration.

In rejecting the claims, the Examiner states that "[i]t would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have used the polycation, protamine, and single stranded DNA taught by Hanson et al. in place of the poly-lysine for the production and use of polyelectrolyte complexes disclosed by Wolfert et al." The Examiner cites the passage on page 273, 1st column, lines 9-13 of the Wolfert et al. reference as providing the motivation to combine the Wolfert et al. and Hanson et al. references. This passage reads: "[c]onjugates formed using the lowest molecular weight polycations appear to be better tolerated than those formed with higher molecular weight poly(L)lysine and they are proposed as candidates for further development". Presumably, the Examiner interprets this passage as saying that poly(L)lysine is not suitable and that other polycations must be found. This interpretation, however, is not supported by the overall disclosure of the Wolfert et al. reference. In fact, the sentence immediately following the passage cited by the Examiner states the exact opposite. In column 1, lines 14 and 15, the Wolfert et al. reference states (with emphasis added): "Having identified a ***suitable*** structure for the DNA-condensing terminal block of the proposed block copolymer structure, we plan now to incorporate...." Thus, a more accurate interpretation of the passage cited by the Examiner is simply that for a polycation (such as poly(L)lysine) a lower molecular weight appears to be

better tolerated.

The Hanson et al. reference also does not provide any motivation for combining the Wolfert et al. and the Hanson et al. references. In fact, the Hanson et al. patent teaches away from such a combination. As set forth above, the Hanson et al. reference teaches a solution of a nucleic acid and a substance having a nucleic acid binding moiety, wherein no particles are precipitated. Thus, the Hanson et al. patent teaches away from forming a "synthetic particle" or "synthetic particles", as is recited in independent claims 28, 37 and 48. In this regard it should be noted that (as set forth above), the Hanson et al. patent teaches adding chaotropic agents (salts) to the solution to prevent precipitation. Thus, the Hanson et al. patent teaches away from the method of claim 37, wherein the protein and the nucleic acid sequence or nucleic acid derivative sequence are provided in "salt-free" solutions. As set forth in MPEP 2141.02 (with emphasis added), "A prior art reference must be considered in its entirety, i.e., as a whole, ***including portions that would lead away from the claimed invention***".

Since the Wu et al. reference is also directed to solutions and not the formation of synthetic particles, Applicants submit that the Wu et al. reference also does not provide the motivation to make the combination proposed by the Examiner. Since the Zobel et al. reference does not even mention arginine, Applicants submit that the Zobel et al. reference also does not provide the motivation to make the combination proposed by the Examiner.

Since the Wolfert et al. reference does not provide any motivation to combine the Wolfert et al. reference and the Hanson et al. reference, and the other references do not provide the motivation either, and in fact teach away from the combination, Applicants submit that there is no motivation to combine the Hanson et al. reference with the Wolfert et al. reference. For at least this reason, Applicants

submit that the Examiner has failed to establish a prima facie case of obviousness for independent claims 28, 37 and 48.

Even if the Wolfert et al. reference and the Hanson et al. reference were combined as proposed by the Examiner, the resulting combination would fail to disclose all of the features of independent claims 28, 37 and 48. As set forth above, the Hanson et al. reference discloses the substance with nucleic binding moiety as comprising polylysine and galactose, but does not disclose the relative proportions thereof. Thus, if the substance with nucleic binding moiety of the Hanson et al. reference was produced with protamine instead of the preferred polylysine, there is nothing in the Hanson et al. patent that would indicate the substance as "comprising more than 50 percent by weight of arginine", as is recited in independent claims 28, 37 and 48. Thus, even if the Hanson et al. reference was combined with the Wolfert et al. reference as proposed by the Examiner, the resulting combination does not show a protein "comprising more than 50 percent by weight of arginine", as is recited in independent claims 28, 37 and 48.

Since the the Wu et al. reference does not disclose the relative amounts of the DNA-binding agent and the binding agent specific to the target cell in the carrier, the Wu et al. reference fails to cure the foregoing deficiency of the combination of the Hanson et al. patent and the Wolfert et al. reference. Since the Zobel et al. reference does not even mention arginine, the Zobel et al. reference also fails to cure the foregoing deficiency of the combination of the Hanson et al. patent and the Wolfert et al. reference.

Since the references cited by the Examiner (alone and in combination) fail to disclose all of the features of independent claims 28, 37 and 48, Applicants submit that the Examiner has, for this additional reason, failed to establish a prima facie case of obviousness for independent claims 28, 37 and 48.

For at least the foregoing reasons, Applicants submit that independent claims 28, 37 and 48 are patentable over the Wolfert et al. reference, the Hanson et al. reference, the Wu et al. reference and the Zobel et al. reference (alone or in combination). Applicants consider it apparent that claims 29-33, 35, 36, 38-47, and 49-53 are also patentable over the foregoing references because they all depend from claims 28, 37 or 48 and recite additional novel features of the present invention.

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If clarification of the amendment or application is desired, or if issues are present which the Examiner believes may be quickly resolved, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. WFG-12544.

Respectfully submitted,
RANKIN, HILL, PORTER & CLARK LLP

By: _____
Paul R. Katterle, Reg. No. 36563

700 Huntington Building
925 Euclid Avenue
Cleveland, Ohio 44115-1405
(216) 566-9700
Customer No. 007609